

Divergent effects of acute exercise and endurance training on UCP3 expression

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letters to the editor

The following is the abstract of the article discussed in the subsequent letter:

Jones, Terry E., Keith Baar, Edward Ojuka, May Chen, and John O. Holloszy. Exercise induces an increase in muscle UCP3 as a component of the increase in mitochondrial biogenesis. *Am J Physiol Endocrinol Metab* 284: E96–E101, 2003. First published September 17, 2002; 10.1152/ajpendo.00316.2002.—Previous studies have indicated that exercise acutely induces large increases in uncoupling protein-3 (UCP3) in skeletal muscle, whereas endurance training results in marked decreases in muscle UCP3. Because UCP3 expression appears to be regulated by the same mechanism as other mitochondrial constituents, it seemed unlikely that exercise would result in such large and divergent changes in mitochondrial composition. The purpose of this study was to test the hypothesis that major changes in UCP3 protein concentration do not occur independently of mitochondrial biogenesis and that UCP3 increases as a component of the exercise-induced increase in mitochondria. We found a large increase in UCP3 mRNA immediately and 3 h after a bout of swimming. UCP3 protein concentration was increased ~35% 18 h after a single exercise bout, ~63% after 3 days, and ~84% after 10 days of exercise. These increases in UCP3 roughly paralleled those of other mitochondrial marker proteins. Our results are consistent with the interpretation that endurance exercise induces an adaptive increase in mitochondria that have a normal content of UCP3.

Divergent effects of acute exercise and endurance training on UCP3 expression

To the Editor: The primary physiological function of mitochondrial uncoupling protein-3 (UCP3) is not yet known. Because of its homology with UCP1, it has been hypothesized that UCP3 is involved in the regulation of energy expenditure in skeletal muscle. Therefore, the effect of exercise and endurance training on UCP3 expression has been extensively studied. These studies unequivocally show that UCP3 mRNA expression is transiently upregulated after an acute bout of exercise (4–6, 14), an effect largely accounted for by increased free fatty acid levels (10). Recently, Jones et al. (3) confirmed this finding, showing that, in rats, UCP3 mRNA was increased acutely and 3 h after a single exercise bout. Jones et al. also reported a marked ~63 and ~84% increase in UCP3 protein after 3 and 10 days of endurance training, respectively. These findings have led the authors to conclude that “endurance exercise results in an increase in UCP3 protein in skeletal muscle as a component of the exercise-induced increase in mi-

tochondrial biogenesis” (3). In this case, however, their conclusion is in contrast with the generally observed finding of decreased UCP3 mRNA and protein levels following endurance training (1, 7, 8, 11–14). For example, Boss et al. (1) showed downregulation of UCP3 mRNA after 8 wk of endurance training in rats (1). In humans, these findings are extended to the protein level, showing decreased UCP3 protein content in trained athletes (7) and after training (11). What can be the reason for the discrepancy between these studies and the conclusion of Jones et al.? Jones et al. show that UCP3 is increased by ~35, ~64, and ~84% with a concerted upregulation of cytochrome *c* and citrate synthase (marker proteins for mitochondrial density). Thus, if the upregulation of UCP3 related to the actual mitochondrial density, the more obvious conclusion would have been that the 10-day training program did not affect mitochondrial UCP3 content. Papers showing declined UCP3 protein levels following training have a cross-sectional (7) rather than a longitudinal design. In longitudinal designs, declined UCP3 levels have been reported after a 14-day training period (9) or longer (11). At present, there is paucity of data about the precise triggers, conditions, and time frame related to training-induced downregulation of UCP3. It therefore cannot be ruled out that the training intervention applied by Jones et al. is of insufficient duration to detect a training-induced decline in UCP3. Moreover, the divergent effect of acute exercise and training on UCP3 mRNA expression perfectly illustrates the importance of the time frame of sampling. Tsuboyama-Kasaoka et al. (14) showed profound upregulation of UCP3 mRNA 3 h postexercise and a return to pretraining levels within 22 h, and reduced levels were recorded 44 h postexercise. In the study by Jones et al., increased UCP3 protein with undetectably low mRNA levels (i.e., very low transcriptional activity) was reported 18 h after a single exercise session. It is therefore conceivable that the protein levels will decrease after the 18-h period. Because Jones et al. sampled muscles 18–20 h postexercise, it is likely that the mRNA data, and possibly protein levels reported, are biased by the remnant effect of the final exercise bout.

In summary, we think that the paper by Jones et al. (3) is compatible with previous studies. The lack of increase in UCP3 when expressed per mitochondria and the undetectably low mRNA levels 18 h postexercise make it feasible that, in the long term (depending on the UCP3 half-life time), decreased

UCP3 protein levels will be detected after endurance training. Furthermore, this study again stresses the importance of considering the remnant effect of the final exercise bout when studying the effects of endurance training. Indeed, in previous papers from the same laboratory in which the same protocol was used, it was shown that the training-induced increase in GLUT4 was almost completely abolished within 40 h postexercise (2).

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REPLY

To the Editor: Drs. Hesselink and Schrauwen say, in their letter entitled *Divergent effects of acute exercise and endurance training on UCP3 expression*, that our findings show that “. . . if related to actual mitochondrial density, the more obvious conclusion would have been that the 10-day training program did not affect mitochondrial UCP3 content.” This is exactly what we concluded: “These increases in UCP3 roughly paralleled those of other mitochondrial marker proteins. Our results are consistent with the interpretation that endurance exercise induces an adaptive increase in mitochondria that have a normal content of UCP3.” So we do not understand what is meant by “. . . the more obvious conclusion would have been. . . .”

Mitochondrial biogenesis is regulated and coordinated by the transcriptional coactivator PGC-1 (3, 6). The uncoupling proteins (UCPs) are among the mitochondrial proteins that increase and are incorporated into mitochondria in response to increases in PGC-1 (3, 6). PGC-1 protein increases in muscle in response to exercise and, likely, mediates the adaptive increase in mitochondria in skeletal muscle (1). In addition, the peroxisome proliferator-activated receptor- α (which is coactivated by PGC-1) is activated by fatty acids and mediates an increase in the mitochondrial enzymes involved in the oxidation of fatty acids (2, 5). Apparently, an increase in UCP3 is a component of this response (4). Each bout of exercise induces increases in PGC-1 expression and in plasma fatty acid concentration that result over time in an increase in muscle mitochondria. In this context, the suggestion that mitochondria undergo an enormous change in mitochondrial composition, with large increases in the enzymes involved in carbohydrate and fat oxidation but a large decrease in UCP3 protein, does not seem plausible.

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